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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LE, EMILY M	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/802,686	VAN NEST, GARY	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,8-10 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,8-10 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/29/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/2007 has been entered.

Status of Claim(s)

2. Claims 2, 6-7 and 11-15 are cancelled. Claims 1, 3-5, 8-10 and 16-18 are pending and under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3-5, 8-10 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a **method of reducing respiratory syncytial virus (RSV) viral load** in an individual who is at risk of being exposed to RSV comprising locally administering a composition to the individual, wherein the administration takes place **about 5 days before** the individual is infected with RSV, wherein the composition comprises a polynucleotide, wherein the polynucleotide is SEQ ID NO: 1.

does not reasonably provide enablement for: a method of suppressing a respiratory syncytial virus (RSV) infection in an individual who is at risk of being exposed to RSV comprising locally administering a composition to the individual, wherein the composition comprises a polynucleotide that is greater than 6 but less than 200 nucleotides in length and comprises the CpG motif, at anytime prior to RSV infection, excluding 3 days before RSV infection, to suppress the infection.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As previously noted, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Nature of the invention:

The claimed invention is directed at the immunotherapeutic use of oligonucleotides comprising the CpG motif to stimulate the immune system, including the induction of Th1 immune response invoked by the production of Th1 associated cytokines accorded by the CpG motif, to suppress RSV infection in a subject being at risk of RSV infection.

Breadth of the claims:

The breadth of the claims is directed to the local administration of a genus of polynucleotides to a host, between 3 to 14 days prior to RSV infection, to suppress the infection. According to the specification, suppressing viral infection "indicates any aspect of viral infection, such as viral replication, time course of infection, amount (titer) of virus, lesions, and/or one or more symptoms is curtailed, inhibited or reduced in an individual. [Paragraph 0030 of U.S. PreGrant No. 20010046967.]

Presence or absence of working examples:

Example 2 of the disclosure provides that intranasal administration (local administration) of a composition comprising a polynucleotide that is SEQ ID NO: 1 to an

individual, cotton rats, 3 days before RSV infection, reduces RSV viral titer in said rats. Hence, the claims are enabling for this scope of the claimed invention. However, the specification does not contain any additional working examples supporting or evidencing the use of any other polynucleotides in suppressing or reducing viral titer in an individual at risked of being infected with RSV. Nor has the specification provided any evidence that the administration of the SEQ ID NO: 1 3 days prior to RSV infection is effective at suppressing or reducing viral titer in an individual at risked of being infected with RSV. In fact, from the same working example, Applicant teaches that the local administration of **SEQ ID NO: 1** to an individual at risk of RSV infection **is not effective in suppressing RSV infection** when the individual is challenged with RSV about 30 minutes after the local administration of SEQ ID NO: 1.

It should further be noted that the specification does not contain working example evidencing the administration of SEQ ID NO: 1 or any other polynucleotide suppresses viral replication, time course of infection, lesions, or one or more symptoms is curtailed, inhibited or reduced in an individual.

State of the art:

As previously stated, the involvement of a Th1 type immune response in combating against intracellular pathogens is a well-recognized general concept. The art acknowledges the importance of Th1 type immune response, which is stimulated by the production of Th1 associated cytokines, in the elimination of intracellular pathogens, including viruses. However, the art has not accredited or recognized any one particular Th1-associated cytokine to the treatment, prevention and suppression of viral infection

in a subject. Specifically, the art teaches that while cytokines secreted by T helper cells are of critical importance for the outcome of many infectious diseases, the production of the "**right**" set of cytokines can be a matter of life or death, as noted by Infante-Duarte et al. Infante-Duarte et al. further notes that in addition to a Th1 type immune response, a Th2 type immune response is also necessary. Specifically, Infante-Duarte et al. teaches that a tight control over where and when Th1 and Th2 immune responses happen is necessary to keep intracellular infections under control, and to prevent the Th1 type immune response from causing damage to the host.[1] Hence, while the importance of a Th1 type immune response is well recognized in the art, the art further notes that a balance between Th1 and Th2 type immune responses is necessary to resolve an infection.

The cytokine art also provides that the efficacy of Th1 associated cytokines, such as interleukin 2, interleukin 12 and interleukin 18, against intracellular pathogens are controversial, as evidenced by Aoki et al.,[2] Bohn et al.,[3] Sakao et al.,[4] Zaitseva et al.,[5] and Masihi, K.[6] Aoki et al. teaches that while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection. Bohn et al. teaches that

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[1] Infante-Duarte et al., Th1/Th2 balance in infection. Springer Seminars in Immunopathology, 1999, 21: 317-338. [Paragraph bridging pages 321-322, in particular.]
[2] Aoki et al. Use of cytokines in infection. Expert Opin. Emerg. Drugs, 2004, vol. 9, No. 2, 223-236. [Lines 4-15, left column, page 229,in particular]
[3] Bohn et al., Ambiguous role of interleukin-12 in Yersinia enterocolitica infection in susceptible and resistant mouse strains. Infect. Immune., 1998, Vol. 66, 2213-2220. [Abstract, in particular.]
[4] Sakao et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int. Immunol., 1999, Vol. 11, 471-480. [Abstract, in particular.]
[5] Zaitseva et al. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to human immunodeficiency virus type 1 infection. Blood, 2000, Vol. 96, 3109-3117. [Abstract, in particular]

interleukin-12, a Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation of a disease. Specifically, Bohn et al. notes that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice. Sakao et al. teaches that interleukin 18, a Th1 associated cytokine, is responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18. Zaitseva et al. teaches that both interleukin 6 and interferon gamma augment the susceptibility of monocyte-derived macrophages to infection. Masihi, K. notes that interleukin 2 increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies. In summation, the art teaches that cytokines can be inherently toxic, have unclear pharmacological behavior and also have pleiotropic effects. Hence, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated.

Additionally, while the art teaches that oligonucleotides containing the CpG motif are capable of stimulating a Th1 type immune response, however, the art also teaches that the **Th1 associated cytokine profile for these oligonucleotides vary from one oligonucleotide and species of subject to the next**, as evidenced by Krieg et al.[7] and Mutwiri et al.[8] Krieg et al notes that **each oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of**

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[6] Masihi, K. Fighting infection using immunomodulatory agents. Expert Opin. Biol. Ther., 2001, Vol. 1, No. 4, 641-653. [Lines 15-25, left column of page 646, in particular]

[7] Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [paragraph that bridge pages 716-717, in particular.]

[8] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90.]

immune stimulation induced by these oligonucleotides varies. Krieg et al. particularly notes that **the type of cytokine stimulated by oligonucleotides containing the CpG motif is distinct from one oligonucleotide to the next**. Additionally, both Krieg et al. and Mutwiri et al. note that **the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif; ii) the spacings between CpG motifs; iii) the numbers of CpG motifs in an oligonucleotide; iv) the absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG motif is presented in the sequence**.

The CpG art further teaches that **the immunostimulatory activity of oligonucleotides containing the CpG is very species specific**, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the *in vitro* immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif. Specifically, Mutwiri et al. notes that the GTCGTT motif, which is the optimal motif for humans, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens; whereas the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice.

Furthermore, both Krieg et al. and Mutwiri et al. sets forth that the recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 associated cytokines. However, Mutwiri et al. provides that TLR-9 has

only been identified in mice and humans. Mutwiri et al. also provides that the TLR-9 is differentially expressed in humans and mice. Hence, if the recognition of the CpG motif were dependent of TLR-9, then it would logically follows that the extent of the Th1 type immune response induced by the oligonucleotide would necessarily vary from one species to the next. Mutwiri et al. also sets forth that *in vitro* observations do not accurately predict what happens *in vivo*.

Moreover, the potential use of oligonucleotides containing the CpG motif to stimulate a Th1 type immune response that treats, prevents and suppresses infection is widely speculated in the art. However, efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive, as evidenced by Yamamoto et al.,[9] Equils et al.,[10] Agrawal et al.,[11] and Olbrich et al.[12] Yamamoto et al. reports that oligonucleotides containing the CpG motif failed to improve the survival in mice challenged with influenza. Equils et al. teaches that such oligonucleotides can induce the HIV transcriptional regulatory elements in long terminal repeats, increasing viral replication. Agrawal et al. teaches that HIV-infected humans treated with oligonucleotides containing the CpG motif showed dose-dependent increases viral load. Lastly, Olbrich et al. teaches that the administration of oligonucleotides containing the CpG motif accelerated and increased the severity of

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[9] Yamamoto et al., Oligodeoxyribonucleotides with 5'ACGT-3' or 5TCGA-3 sequence induce production of interferons. Curr. Top. Microbiol. Immunol. 2000, Vol. 247, 23-40.
[10] Equils et al. Toll-like receptor 2 (TLR2) and TLR9 signaling resulted from HIV-long terminal repeat transactivation and HIV replication in HIV-1 transgenic mouse spleen cells: implications of simultaneous activation of TLRs on HIV replication. J. Immunol. 2003, 170, 5159-5164.
[11] Agrawal, et al. Was induction of HIV1 through TLR9? J. Immunol. 2003, 171, 1621-1621.

Friend retrovirus in mice. In the case of Olbrich et al., the author notes that the use of oligonucleotides containing the CpG motif for the treatment of viral infection may be a double edge sword that can resolute in effective therapy but also in acceleration of disease. Olbrich et al. notes that this double edge sword observation may be dependent on the time point of treatment.

Hence, overall, the literature notes the use of CpG to stimulate the production of cytokines, the use of cytokines to influence viral infection, and the development of a treatment regimen for diseases is unpredictable and complicated.

Amount of guidance or direction provided:

However, the working examples provided in the specification do not set forth any guidance or directions relating to the **effective use** of other polynucleotides to suppress RSV infection in an individual. As noted in the art, **Th1 associated cytokine profile for these oligonucleotides vary from one oligonucleotide and species of subject to the next**. Applicant has not even characterized the Th1 profile induced by the polynucleotide of SEQ ID NO: 1 and render a reasonable analysis, through a representative number of working embodiments, that polynucleotides capable of inducing the same Th1 profile would also be effective in suppressing RSV infection in an individual at risk of being exposed to RSV infection. All that Applicant has provided are conjectures that all polynucleotides comprising the CpG motif, which is recognized in the art to have immunostimulatory activities, could be used to suppress RSV infection in an individual at risk of being infected with RSV. However, it should be noted that

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[12] Olbrich et al. Preinfection treatment of resistant mice with CpG oligodeoxynucleotides renders them susceptible to friend retrovirus-induced leukemia. J. Virol., 2003, 77, 10658-10662.

none of these conjectures are substantiated by any data or evidence that would reasonable allow the skilled artisan to believe that any polynucleotides comprising the CpG motif would be effective in suppressing RSV infection in an individual at risk of being exposed to RSV infection. In the instant case, in light of the art, the skilled artisan would readily art acknowledges the importance of Th1 type immune response, which is stimulated by the production of Th1 associated cytokines, in the elimination of intracellular pathogens, including viruses. However, the skilled artisan would not readily accept and believe that the stimulation of any Th1 immune response would be effective in suppressing a RSV infection in an individual at risk of RSV infection because the skilled artisan knows the importance of inducing the right set of cytokines, the right Th1 profile. In the absence of the identification of the Th1 profile that leads to the suppression of RSV infection in an individual at risk of RSV infection, the skilled artisan would not be able to practice the claimed invention without undue burden of experimentation. In the instant case, the skilled artisan would have to ascertain the Th1 profile that is necessary to suppress RSV infection in the individual and experiment with all polynucleotides having the CpG motif to determine if the Th1 profile produced from these polynucleotides is the same with the Th1 profile necessary to suppress RSV infection in an individual at risk of RSV infection. In the instant case, while it may appears that the work imposed upon the skilled artisan is routine experimentation, however, it should be noted that this is not the case. In this case, the skilled artisan would be required to perform the research and experimentation that Applicant should have all ready provided in the specification, at the time the invention was filed.

Applicant is reminded that the disclosure provided in the specification is **limited** to one protocol, reducing RSV viral titer in an individual at risk of RSV infection with the local administration of SEQ ID NO: 1. Applicant has not provided a disclosure that commensurate in scope with the claimed invention. In view of the high level of unpredictability known in the Th1, cytokine and CpG arts, it is found that the skilled artisan would not be able to practice the claimed invention without the burden of undue experimentation. Additionally, it should be noted that the working examples do not set forth any guidance or directions relating to the **effective use** of other treatment protocols, i.e., the time period in which the polynucleotide can be locally administered to effectively suppress RSV infection. In both instances, the only thing that the disclosure provides is suggestions directed to the use of other polynucleotides and other various treatment protocols. However, none of these suggestions are substantiated by any data or evidence.

Predictability or unpredictability of the art:

As discussed above, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated. The art also recognizes that use of CpG to stimulate cytokine production, the use of the induced cytokine to influence viral infection, and the development of treatment regimen is unpredictable and complicated. **The art additionally teaches that the efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive**.

Quantity of experimentation necessary:

Extreme undue burden of experimentation would be imposed upon the skilled artisan practicing the full scope of the claimed invention. As stated above, Applicant has not provided much guidance or direction relating to the claimed invention. All that Applicant has provided is a conclusion that is made on the basis of generalized concepts that are well known in the art. Generalized concepts are directed to support a general direction of studies or research; however, they do not support concrete conclusions. Concrete conclusions must be substantiated by facts, including evidence. In the instant, while the general direction of research may be outlined for the skilled artisan, however, due to the high level of unpredictability noted in the art, the skilled artisan would not readily be able to practice the claimed invention without the undue burden of experimentation. The path that the skilled artisan must take in his research is marked with many challenges that are recognized in the art, including the complex nature of oligonucleotides containing CpG motif and the complexity of the immune system, including the Th1 type immune response and the functional characteristics of its associated cytokines. Hence, in view of the lack of any guidance in the specification concerning the effective use of oligonucleotides to suppress RSV infection in an individual at risk of RSV infection; the unpredictability of oligonucleotides containing CpG motif to stimulate specific immune response; and the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of cytokines; the skilled artisan would not be able to reasonably practice the claimed invention without an undue burden experimentation. Thus, the claims stand rejected.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Response to Applicant's Arguments

5. In response to the rejection, Applicant argues that the specification, page 17, teaches structural and sequence characteristics of an immunostimulatory sequence comprising the sequence 5'TCG3', wherein the polynucleotide is grater than 4 and less than about 200 nucleotides. Applicant also argues that immunostimulatory sequences are described in the art and may readily be identified using standard assays which indicate various aspects of the immune response, such as cytokine secretion, antibody production...etc. Applicant further argues that the specification teaches an assay to determine whether an immunostimulatory sequence is administered in an amount sufficient to suppress an RSV infection.

Applicant's arguments have been considered, however, it is not found persuasive. While it is noted that the disclosure does contain lengthy teachings directed at structural and sequence characteristics of an ISS, however, none the teachings commensurate with the claimed invention. That is, the disclosure does not teach of any immunostimulatory sequence that is effective in suppressing, to the full breadth of the term "suppressing", as defined in the specification. All that Applicant has provided is that SEQ ID NO: 1 reduces RSV viral load in cotton rats, when administered 3 days

prior to RSV infection. Moreover, while immunostimulatory sequences are described in the art and may readily be identified using standard assays, the immunostimulatory sequences encompassed by the claimed invention may not readily be ascertained as alleged by Applicant. In the instant case, Applicant has not set forth the cytokine secretion profile that the immunostimulatory sequence must have in order to render it effective in suppressing RSV infection. In the absence of a cytokine profile, the skilled artisan would not readily be able to arrive at the claimed invention, nor would the skilled artisan would readily believe that any immunostimulatory sequence, having the TCG motif can be administered to suppress RSV infection. As noted by Krieg et al., each immunostimulatory sequence is distinct from one another because of the cytokine profile induced. Additionally, it should further be noted that while Krieg et al. does recognize that immunostimulatory sequences have similar properties, in general, such as the induction of a Th1 biased immune response and activation of NK cells, Krieg et al. further note that each immunostimulatory sequence has to be considered as a separate agent because of the distinct cytokine profile induced. This is further evidenced by Mutwiri et al. Mutwiri et al. states that the **specific purines and pyrimidines surround the CpG motif in the immunostimulatory sequence, as well as spacings between CpG motifs may influence both the level and type of immune stimulation**. Furthermore, Mutwiri et al. clearly demonstrates that the immunostimulatory activities induced by immunostimulatory sequences are further varied among species, as indicated in Table 1 of Mutwiri et al.

Applicant is reminded that the enablement rejection is made on the basis of the wands factors, as a whole, rather than any one of the factors. In the instant case, the issue is not whether the disclosure has disclosed what is known in the art, such as how to determine whether an immunostimulatory sequence is administered in an amount sufficient to suppress an RSV infection and identified using standard assays which indicate various aspects of the immune response; rather, the issue here is that the disclosure has failed to disclose what is not known in the art. In the instant case, the art does not teach the use of any immunostimulatory sequence to suppress RSV infection. All that the art teaches is the recognized used of immunostimulatory sequence as an adjuvant. The use of immunostimulatory sequences as an adjuvant is not comparable in scope with the use of immunostimulatory sequences to suppress RSV infection. Applicant has failed to provide any guidance relating to the therapeutic use of immunostimulatory sequences to suppress RSV infection.

In addition to above, it is noted that Applicant has taken issues with several arts cited by the Office, indicating that none are relevant because none discusses RSV. This argument has been considered, however contrary to Applicant's position, the cited arts are relevant. While these references are not specific to RSV, they are specific to the use of immunostimulatory activities, including those induced by immunostimulatory sequences. These arts set forth the challenges and unpredictability encountered with the attempted use of immunostimulatory activities. These arts also set forth the difficulties of harnessing the activities induced by immunostimulatory sequences.

Thus, in view of the discussion, the rejection is maintained.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. The double patenting rejection over U.S. Patent Application No. 10/426237 is withdrawn in view of the abandonment of the cited patent application.

8. The double patenting rejection over U. S Patent No. 10/898512 is maintained for reason(s) set forth in the record. It is noted that Applicant has stated that Applicant will address this provisional double patenting rejection with a terminal disclaimer. Applicant's intention is noted. Until the rejection is properly addressed with a terminal disclaimer, the rejection is maintained on the record.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Emily M. Le/
Patent Examiner
Art Unit 1648

/E.Le/